Signaling by the TGF β Superfamily

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The transforming growth factor β (TGF β) superfamily was discovered in a hunt for autocrine factors secreted from cancer cells that promote transformation (Roberts et al. 1981). However, it soon became clear that TGF β and the related bone morphogenetic proteins (BMPs) regulate diverse developmental and homeostatic processes and are mutated in numerous human diseases. Furthermore, TGF β -superfamily members such as activins, Nodal, and growth differentiation factors (GDFs) were shown to control cell fate as a function of concentration, thus defining them as a key class of secreted morphogens (Green and Smith 1990).

TGF β -superfamily members are highly conserved across animals and comprise the largest family of secreted morphogens. Ligands are produced by cleavage of a pro-domain that releases active disulfide-linked homo- or heterodimers. TGF β (plus activin, Nodal, and GDFs) and BMPs both signal through transmembrane serine/threonine kinase receptors. These are typically presented as using distinct downstream pathways (see Figs. 1 and 2), although some crosstalk in certain cell types occurs. In each pathway there are two kinds of receptors: type I and type II (Massague 1998). Ligand binding induces formation of heterotetramers containing two type II and two type I receptors, which allows the constitutively active type II receptor to phosphorylate a glycine-serine (GS)-rich region in the type I receptor. This initiates signaling through the Smad pathway (Fig. 1), with the phosphorylated GS region providing a docking site for receptor-regulated Smad proteins (R-Smads). In TGF β signaling, this is promoted by Smad anchor for receptor activation (SARA) in the endosomal compartment (Attisano and Wrana 2002).

Despite the large TGF β superfamily (>30 members in humans), the receptor repertoire is limited: only five type II and seven type I receptors are encoded in mammalian genomes, with the type I receptors funneling signaling into one of two distinct R-Smad pathways: the TGF β -Smad pathway (R-Smad2/3) or the BMP-Smad pathway (R-Smad1/5/8) (Massague 2012). Docking of R-Smads allows

phosphorylation of the last two serines in their carboxyl termini by the type I kinase, which induces dissociation from the receptor, binding to the common Smad, Smad4, and nuclear accumulation of the Smad complex. In the nucleus, most Smads regulate transcriptional responses by direct binding of their MH1 domain to DNA (Smad2 only binds to DNA indirectly) in cooperation with various DNA-binding partners that include sequence-specific transcription factors. These Smad DNA-binding partners typically bind to the R-Smad, thus maintaining specificity of the transcriptional response. Smads also interact with transcriptional coactivators or corepressors that modulate the transcriptional output. Interestingly, the remaining two Smads, Smad6 and Smad7, are transcriptional targets of R-Smads and act in a negative-feedback loop to inhibit signaling by interacting with the receptors and recruiting Smurf and related ubiquitin ligases of the Nedd4 family to induce receptor degradation. SnoN and the related Ski, as well as Arkadia, a ring-finger ubiquitin ligase (also known as RNF111), are important examples of negative and positive regulators of Smad2/3-dependent transcription, respectively (Stroschein et al. 1999; Niederlander et al. 2001). SnoN and Ski negatively regulate the pathway as corepressors of Smads, whereas Arkadia promotes signaling by degrading negative regulators of the pathway, such as Smad7 and SnoN/Ski.

The Smad pathways are the major mediators of transcriptional responses induced by the TGF β family, which control cell-fate determination, cell-cycle arrest, apoptosis, and actin rearrangements. However, receptor signaling is not restricted to R-Smad activation (Fig. 2). The type II receptor phosphorylates Par6 polarity proteins bound to the type I receptor to dissolve tight junctions in epithelial cells (Ozdamar et al. 2005) and specify axons (Yi et al. 2010). Furthermore, protein phosphatase 2A (PP2A) is regulated by the receptors (Griswold-Prenner et al. 1998), signaling via SHC-Grb2 has been reported (Lee et al. 2007), and interactions between the kinase PAK and the TGF β receptor link it to cytoskeletal and focal adhesion dynamics

Figure 1. Smad signaling.

(Wilkes et al. 2009). BMPRII is of particular interest because it has a unique carboxy-terminal tail that serves as a docking site for binding of the kinases LIMK and JNK, thus linking BMP signaling to the actin cytoskeleton and the microtubule network, respectively (Miyazono et al. 2010; Podkova et al. 2010). These pathways are critical in neuronal dendritogenesis and may be important in familial pulmonary hypertension, in which mutations in BMPRII are a major cause of disease (Morrell 2011). Numerous kinase cascades, including the ERK, JNK, and p38 MAPK path-

ways, are also regulated by TGF β signaling (Mu et al. 2012), with signaling to TRAF6 being one important mechanism of MAPK regulation. These non-Smad pathways combine with the gene-expression programs controlled by Smads to yield an integrated response to TGF β signals.

Finally, TGF β signaling is embedded in a higher-order network of interactions with other signaling pathways. For example, Smads interact with the Wnt pathway (via Lef/TCF transcription factors and β -catenin), the Hedgehog pathway (via Gli transcriptional regulators), and the Hippo

Figure 2. Non-Smad signals.

pathway (via TAZ and YAP). This provides an integrated signaling network that allows contextual interpretation of morphogen signals in diverse biological settings (Attisano and Wrana 2013).

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